Treatment of Nausea and Vomiting During Chemotherapy

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Abstract

Nausea and vomiting are two of the most troubling adverse effects patients experience during chemotherapy. While newly available treatments have improved our ability to manage nausea and vomiting, anticipatory and delayed nausea and vomiting are still a major problem for patients receiving chemotherapy. Many cancer patients will delay or refuse future chemotherapy treatments and contemplate stopping chemotherapy altogether because of their fear of experiencing further nausea and vomiting. The purpose of this article is to provide an overview of the patho-psychophysiology of chemotherapy-induced nausea and vomiting and the recommended guidelines for treatment.

Keywords

Cancer, chemotherapy, nausea, vomiting

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Cancer treatments are quite challenging for cancer patients to endure. The cancer treatments and subsequent adverse effects patients experience often make them feel worse than the disease itself.[1–3] Chemotherapy-induced nausea and vomiting (CINV) are two of the most common and troublesome adverse effects experienced by cancer patients.[1–3] Cancer patients will delay chemotherapy treatments and contemplate refusing future treatments because of fear of further CINV.[1–4]

While significant advances have been made in the treatment of acute chemotherapy-induced vomiting (CIV), chemotherapy-induced nausea (CIN), anticipatory nausea and vomiting (ANV), and delayed nausea and vomiting (DNV) remain substantial problems for cancer patients.[1,2] Anticipatory nausea is reported by 30 % of patients who experienced nausea during earlier chemotherapy treatment cycles.[1] Anticipatory vomiting is reported in 20 % of patients who experienced vomiting during earlier chemotherapy treatment cycles.[5,6] Anticipatory, acute, and delayed CINV lead to poorer chemotherapy adherence, impaired function, increased anxiety and depression, and diminished quality of life among patients.[4,7–9] In turn, physicians and patients increase usage of healthcare resources to manage these adverse effects, substantially increasing the public health burden of cancer and its effective treatment.[2–9]

The purpose of this article is to provide an overview of the patho-psychophysiology of CINV and the recommended guidelines for its treatment.

Pathophysiology of Chemotherapy-induced Nausea and Vomiting—The Role of Neurotransmitters

CIN and CIV are distinct symptoms; however, they often go hand in hand and are among the most unpleasant adverse effects of most chemotherapy regimens for cancer patients. It is important to note that nausea can occur without vomiting. CINV can be acute (during the first 24 hours post-treatment) and delayed (after the first 24 hours post-treatment and up to five to eight days post-treatment).[10] CINV, once experienced during early chemotherapy cycles, can create a conditioned response that leads to anticipatory nausea in future cycles of treatment.[11] Many of the clinical symptoms commonly reported by patients in association with nausea are manifestations of autonomic nervous system activity in response to chemotherapy delivery. For example, physical manifestations such as pallor, sweating, and feeling hot or cold all over commonly precede or accompany nausea.[7,12] Vomiting is a reflex triggered by toxic substances, such as chemotherapeutic agents, causing cell damage within the stomach and small intestines. Broadly, these agents are sensed in the gastric or small bowel mucosa and cause stimulation of vagal afferents that interact with the hindbrain of the central nervous system (CNS), resulting in efferent vagal action that ultimately leads to an emetic response.

Numerous classic neurotransmitters affect the emetic response, including serotonin, substance P, dopamine, acetylcholine, and γ-aminobutyric acid (GABA). Other chemical messengers, acting as neurotransmitters, that affect the emetic response include histamine,

endorphins, and cannabinoids.[13] We know that inhibiting some of these pathways is effective in alleviating chemotherapy-related vomiting, although these same methods have not done a good job of alleviating chemotherapy-related nausea. This suggests that different pathways may play a role in the manifestation of nausea.

The most widely studied compound related to the development of CINV is serotonin, also known as 5-HT. 5-HT is produced by enterochromaffin cells, a unique cell type dispersed throughout the enteric epithelium. These cells constitutively express 5-HT and 5-HT is expressed more abundantly upon exposure to a chemotherapeutic agent. At elevated levels, 5-HT is released from the basal surface into the lamina propria. There, secreted 5-HT binds to cognate 5-HT_3 receptors located on vagus nerve terminals, thus acting as a neurotransmitter transducing a signal to the hindbrain. In turn, the translated signal triggers a motor response of nausea and vomiting, carried by efferenting vagal nerves.[14]

For approximately 30 years, 5-HT_3 antagonists have been extremely useful for curbing nausea and vomiting in patients receiving chemotherapy.[1,15] These drugs exert their anti-emetic potential by competing with 5-HT for binding of 5-HT_3 receptors, thereby blocking a pro-emetic signal to the CNS. The newest 5-HT_3 antagonist, palonosetron, has a higher receptor binding affinity than other commonly used 5-HT_3 antagonists,[7] which makes it more effective at preventing nausea and vomiting. Palonosetron also exhibits allosteric positive cooperativity with the 5-HT_3 receptor compared with other 5-HT_3 antagonists (such as ondansetron and granisetron),[8] and can trigger 5-HT_3 internalization to prolong the inhibitory effects of 5-HT_3 receptor function.[9] Moreover, palonosetron has a half-life of 40 hours, which may allow more effective prevention of delayed nausea and vomiting than can be achieved with the other 5-HT_3 antagonoists.[16] Additionally, palonosetron may act to influence the neurokinin-1 receptor (NK-1) pathway as there is downstream cross-talk between 5-HT_3 and NK-1 receptor pathways.[10]

Since 5-HT synthesis is increased significantly after chemotherapy, another method of potential therapeutic benefit would decrease 5-HT synthesis in the gut. Since 5-HT synthesis is dependent on tryptophan hydroxylase (TPH), this enzyme may represent a viable and more broadly acting target. Pre-clinical studies have been conducted using a TPH inhibitor to selectively inhibit 5-HT in the gut using a ferret model of chemotherapy-induced emesis.[17]

Substance P is another strong regulator of the emetic response; it binds to the NK-1 receptor. Both substance P compound and NK-1 receptor are found within the CNS and also within the gut. Compared with 5-HT/5-HT_3 receptor interaction, less is known about how and where substance P and NK-1 act in promoting emetic potential, although peripheral and central components may be involved. Pre-clinical studies suggest that antagonizing NK-1 receptor action in the CNS is key to preventing nausea and vomiting, as agents not capable of crossing the blood–brain barrier do not protect against emesis.[18] Clinically, administration of aprepitant, the first drug devised to antagonize the NK-1 receptor, has proved effective in preventing NV when combined with 5-HT_3 receptor antagonists.[19–21]

Other pathways controlling the emetic reflex exist, but far less is known about their regulation of the emetic response, especially in CINV. For example, dopamine release and cognate dopamine receptor-2 signaling may play a role, as dopamine antagonists have been shown to be effective in treating nausea and vomiting. Additionally, while participation of the CNS is clearly a major contributor to the emetic process, it is also possible the enteric nervous system itself may be able to control nausea and vomiting effects without CNS interplay. Understanding of the role of mediators in the pathologic development of CINV will advance the development of a broader range of more effective anti-emetic treatments for CINV. Further research on the physiologic mechanisms involved in the development of nausea and vomiting is needed to develop therapies to fully eradicate anticipatory, acute, and delayed CINV.

Pathopsychology of Nausea and Emesis—The Role of Conditioning and Cognition

ANV occurs before chemotherapy infusion. ANV is believed to be a conditioned response, such that ANV will occur only after a patient has experienced nausea and/or vomiting in response to chemotherapy treatment.[22] However, there are reports of ANV developing without an individual previously experiencing post-treatment nausea (e.g. in children).[23] The general understanding of ANV as a conditioned response is that contextual factors, such as the sights, sounds, and smells of the clinic, become conditioned stimuli paired to the unconditioned stimulus (the chemotherapy agent) that produces the unconditioned response (nausea and vomiting). Therefore, the conditioned stimuli come to elicit the conditioned response: nausea and vomiting prior to chemotherapy (ANV). There is support for ANV as a conditioned response through correlational studies,[24–26] as well as through laboratory models in humans and rats.[25,27] ANV has been estimated to occur in roughly 25–30 % of patients,[6,28,29] although there is significant variability among studies.[6,24,29] ANV negatively affects patient quality of life and may interfere with treatment.[6,24]

The 2012 National Comprehensive Cancer Network (NCCN) Guidelines recommend that ANV be prevented through optimal anti-emetic therapy during every cycle of chemotherapy.[22] Despite decreases in the frequency of post-treatment emesis over time, decreases in ANV were not observed in a large community study.[28] Therefore, ANV continues to be a problem for patients despite advances and aggressive treatment with anti-emetics.[28] Unfortunately, pharmacologic interventions typically do not reduce ANV; however, cognitive–behavioral interventions, such as systematic desensitization, can be effective.[11,30] Additionally, conditioning techniques such as overshadowing (pairing a strongly flavored beverage with the beginning of infusion for a couple of cycles and then removing the stimulus at the next cycle) can help alleviate ANV.[25,31]

The conditioning paradigm does not fully account for the development of ANV, and cognitive factors have been identified as contributors to ANV, including anxiety and response expectations.[5,6,11,26,32–36] Anxiety is believed to contribute to ANV, at least in part, through negative expectations.[33,37–39] The relationships between anxiety and negative expectations are reciprocally interactive. For example, increased anxiety produces negative expectations and negative expectations increase anxiety.

Evidence suggests that a patient's expectations of experiencing nausea strongly predict the actual occurrence of ANV.[34,40] It is most likely that a combination of classic conditioning and expectancy theories more fully explain the psychopathology of ANV because conditioning effects are mediated by patient expectations and conditioning effects moderate patient expectations.[41–43]

A patient's expectations of nausea are also a strong predictor of post-treatment nausea even when controlling for other known contributors.[44–50] Individual variation in patient expectations may also explain why the frequency and severity of CINV are different for different patients on the same chemotherapy regimens. These between-patient differences cannot be fully accounted for by the properties of the chemotherapy agents or patient demographic characteristics.[30,50,51] Patient and treatment factors associated with CINV include female gender, younger age, lower alcohol intake history, history of motion sickness, history of emesis during pregnancy, history of CINV, and pre-treatment expectations of nausea.[52] Family conflict has been found to be related to post-treatment nausea and ANV for younger adult and female patients.[53] Additional cognitive and behavioral interventions that focus on changing expectations are needed as adjuncts to standard pharmaceutical anti-emetic therapies to help fully control anticipatory, acute, and delayed CINV. Roscoe and colleagues found that using a cognitive manipulation technique to increase beliefs that acupressure bands could prevent CINV resulted in significantly reduced CINV among patients with high initial expectations of experiencing CINV.[49] These findings enhance our understanding of factors that contribute to CINV. The combined use of techniques such as systematic desensitization, overshadowing, and expectation manipulation with pharmaceutical interventions may lead to more effective management of CINV. More research is needed investigating the psychopathology of CINV to effectively manage the full spectrum of anticipatory, acute, and delayed CINV.

Integrative Medicine Interventions

Integrative medicine approaches, consisting of both complementary and alternative medicine interventions, are commonly used by cancer patients to reduce the toxic adverse effects of chemotherapy treatment. Patients typically use these types of intervention along side their traditional allopathic (e.g. pharmaceutical) interventions. Integrative modalities are used by the majority of patients with cancer and are most commonly used by patients with advanced-stage disease.[54,55] These types of treatment usually do not require a prescription from a physician, can be accessed in the community, and are gaining increasing scientific evidence to support their use.

Herbal Supplements

Ginger is the most abundantly used supplement for the prevention and/or reduction of CINV. Since the 16th century, the dried aromatic rhizome (underground stem) of ginger (*Zingiber officinale*) has been used by practitioners of both Indian (Ayurvedic) and traditional Chinese medicine to treat gastrointestinal upsets such as nausea and excessive flatulence.[56] Ginger has been thoroughly studied and found to be useful for nausea and vomiting associated with motion sickness, surgery, and pregnancy.[57–65] Although ginger has been approved for use to prevent motion sickness in Europe and its use is recommended,[56] ginger is not a US Food and Drug Administration (FDA) approved medicinal treatment in the US. However, ginger is readily available over the counter and in grocery stores as it is not an FDA regulated substance. The FDA currently classifies ginger as a generally regarded as safe substance if consumption is limited to 4 g daily. As previously mentioned, current 5-HT anti-emetic medications are receptor antagonists for specific neurotransmitters in the gastrointestinal tract.[66] Likewise, ginger can bind 5-HT_3 receptors to enhance anti-emetic effects and can increase levels of detoxification enzymes to counteract oxidative damage to tissues.[67] For the best results in reducing CINV, ginger should be implemented before the onset of symptoms or before the first chemotherapy treatment cycle. Our research group previously demonstrated, in a 744-patient phase III randomized, placebo-controlled clinical trial, that three different daily doses of ginger (0.5, 1.0, 1.5 g) plus standard 5-HT_3 receptor antagonists and dexemethasone significantly reduced acute CINV compared with placebo plus standard standard 5-HT_3 receptor antagonists and dexamethasone.[68,690] Our findings suggest that cancer patients can achieve greater alleviation of acute CINV by using ginger supplementation of 0.5–1.0 g daily (equivalent to quarter to half a teaspoon of ground ginger) along with standard 5-HT_3 receptor antagonists and dexamethasone.[68,69] It is important to note that the ginger used in this study consisted of capsules containing a purified liquid extract equivalent to 250 mg ginger. The purified liquid extract concentrated the biologically active components of the ginger root, such as gingerols, zingerones, and shogaols.[57] Unclear forms of ginger, such as crystallized, raw, tea, or aromatherapy, are thought to have similar effectiveness.

Many other herbal supplements, in the form of tea or aromatherapy, have been recommended for the relief of CINV. Cinnamon bark, peppermint, chamomile, fennel, and rosewood are among the most common.[70] Similar to ginger, these herbs have antispasmodic activity and promote digestive health. Studies have shown that citrus bioflavonoids can actually cause nausea and vomiting.[70] Chinese medicinal herbs have demonstrated effectiveness against CINV.[54] Chinese medicinal herbs are highly variable compounds and include any liquid extract of a mixture of herbal compounds used to treat symptoms or diseases. Chinese medicinal herbs are prepared by Chinese medicine practitioners to reduce therapeutic toxicity and/or strengthen the body's resistance and immunity.[54] Usually, Chinese herbalists determine the combination of herbs on an individual basis depending on patient symptoms and conditions. Therefore, a Chinese herbalist as well as an oncologist should be consulted before use of Chinese medicinal herbs. Three published studies favored use of Chinese medicinal herbs for the relief of CINV. Shenqi fuzheng injections (consisting of two herbs),[71] Aidi injections (consisting of four herbs),[72] and Aifukang (consisting of 11 herbs)[73] reduced CINV in a sample of breast cancer patients.[55]

Acupuncture and Acupressure

Acupuncture is another form of traditional Chinese medicine that has been used for centuries to treat nausea and vomiting. Over the past 20 years, clinical evidence has supported the use of acupuncture for CINV.[74] Acupuncture is a 4,000-year-old therapeutic technique that involves inserting and manipulating needles with and without electrical stimulation and providing pressure or electrical stimulation at specific points in the body.[74] Research suggests that acupuncture works primarily on the nervous system through stimulating brain activation or

deactivation, as documented by neuroimaging techniques.[75] Needle insertion points are chosen based on specific anatomic sites associated with specific bodily functions.[75] The acupuncture points most commonly used for control of nausea and vomiting are P6 and ST36.[74] P6 is located between tendons in the wrist approximately two inches proximal to the crease of the wrist. ST36 is on the anterior lateral side of the leg. Traditional acupuncture involves manual manipulation of needles, whereas electro-acupuncture involves applying a small electric current to the needles. Acupressure incorporates acupuncture point stimulation through the use of wrist-worn devices consisting of an elastic band and embedded stud, such as Sea-Bands® (Sea-Band Ltd, Hinckley, UK).[75] Electro-stimulation involves acupuncture point stimulation by an intermittent electrical current similar to units used for pain relief through the use of wrist-worn devices, such as Relief-bands® (Woodside Biomedical Inc., CA).[76] Electro-stimulation units that confer a constant electro-stimulation are not recommended for control of CINV.[76] Although the overall effect of acupuncture strongly suggests effectiveness against acute and delayed CINV, the data are not conclusive. For example, in 2005, Ezzo published a meta-analysis concluding that acupuncture combined with standard anti-emetics significantly reduced acute CINV.[77] However, in 2007, both Gardani[78] and Dibble[79] showed no effect of acupressure on acute CINV. Overall, acupuncture is considered to be a cost-effective, minimal-risk integrative therapy that can be used in conjunction with standard anti-emetic pharmaceuticals for the management of CINV.

Biopsychobehavioral

Biopsychobehavioral interventions such as progressive muscle relaxation, guided imagery, hypnosis, and exercise are also efficacious therapies for the treatment of anticipantory, acute, and delayed CINV. Biopsychobehavioral interventions are especially appropriate and most beneficial if implemented in a preventive manner and started before the first chemotherapy treatment cycle and, most importantly, before the first onset of symptoms of CINV.[80,81]

Progressive muscle relaxation (PMR) involves the tension and relaxation of muscle groups in sequence to relax physically and mentally.[81] PMR alone reduces the severity of nausea associated with chemotherapy.[82] PMR combined with a 20-minute massage during chemotherapy infusions reduces the severity of nausea.[83] Guided imagery, a technique used to focus a patient's attention on a particular image and associated sensory experiences, reduces the incidence of vomiting in the 24 hours after chemotherapy.[84] Patients who use guided imagery combined with an anti-emetic regimen versus an antiemetic alone have a more positive chemotherapy experience.[85] PMR is often combined with guided imagery to treat CINV with consistent, positive outcomes. PMR combined with guided imagery reduces the incidence of nausea[86,87] and vomiting[84,86,87] in the first four days after chemotherapy and the severity of nausea[83,87–91] and vomiting[87,89] up to five days following chemotherapy. Cognitive distraction and systematic desensitization have been used to successfully reduce the severity of ANV[92,93] and CINV.[88,93] Overshadowing is another technique that has been used to help alleviate ANV.[25,31] Teaching self-hypnosis, which typically involves using the imagination to suggest feeling good and feeling safe, reduces the incidence of ANV[92,94] and the severity of CINV[95] in children undergoing chemotherapy. Hypnosis has also been used successfully with adults to reduce ANV.[96]

Several researchers have used exercise interventions to aid in reducing CINV. Aerobic exercise has been shown to help reduce the severity of CINV[97] and yoga has been shown to be beneficial in reducing CINV.[98]

Anti-emetics

Advances in $5HT_3$ antagonists and NK-1 antagonists have dramatically improved control of CINV. Palonosetron (Aloxi®; Eisai Inc., Woodcliff lake, NJ) and aprepitant (Emend®; Merck & Co. Inc., Whitehouse Station, NJ) are the newest anti-emetics.

Palonsetron is a second-generation antagonist of 5-HT_3. Its main advantages compared with the other 5-HT_3 receptors include: its significantly longer half-life (approximately 40 hours, 10 times longer than first-generation 5-HT_3 antagonists, its higher binding affinity, its high selectivity to the 5-HT_3 receptors (with little effect on other receptors), and its excellent safety profile (at even up to three times its FDA approved dose).[99] A single dose (0.25 mg intravenously) of palonosetron can effectively prevent acute CINV resulting from moderately to highly emetogenic chemotherapy.[4,8,9] Recent studies comparing palonosetron with ondansetron and granisetron suggest the superiority of palonsetron on all days, but particularly between 24 and 120 hours after chemotherapy. Complete response rates ranged from 48 to 57 % using 0.75 mg of palonosetron and from only 39 to 45 % when not using it.[100–102] Additionally, Saito and colleagues conducted a prospective, randomized, head-to-head trial between palosetron and granisetron for both acute and chronic CINV in 1,019 patients. This study showed non-inferiority of palonosetron compared with a first-generation 5-HT_3 antagonist in the acute phase of CINV (0–24 hours) and superiority of palonosetron in delayed CINV (24–120 hours).[101] As such, current research supports the use of the second-generation 5-HT_3 receptor antagonist over the first-generation 5-HT_3 receptor antagonists (e.g. ondansetron, granisetron, dolasetron) for the control of acute and delayed CINV for moderately emetogenic chemotherapy agents.[101]

Aprepitant and fosapretitant are potent, selective, NK-1-receptor-competitive antagonists of substance P, believed to be an essential component in triggering the emetic reflex.[103] Aprepitant and fosapretitant can penetrate the CNS where there is a concentration of NK-1 receptors. Aprepitant is a three-day regimen, with a recommended dosage of 125 mg orally on hour prior to chemotherapy treatment (day one) and 80 mg orally once daily in the morning on days two and three. Fosaprepitent is a prodrug of aprepitant for injection (115 mg over 15 minues) and can be substituted for aprepitant 30 minutes prior to chemotherapy on day one only. In 2003, Hesketh et al.[103] published a randomized, double-blind, parallel-group, placebo-controlled trial of 530 patients receiving cisplatin (a highly emetogenic agent). The aprepitant group response was superior to that of the standard therapy group in acute and delayed phases, as well as overall.[103] Subsequently, a prospective, randomized, double-blind, parallel study of 866 patients receiving moderately emetogenic chemotherapy over multiple cycles demonstrated the efficacy of aprepitant in prevention of nausea and emesis over all four cycles of treatment.[104] This randomized, placebo-controlled trial also evaluated daily aprepitant with dexamethasone for three days versus a single daily dose of palonosetron with dexamethasone for acute and delayed CINV. The study demonstrated no statistical significance between groups, suggesting that one dose of aprepitant with a standard anti-emetic regimen has similar effectiveness to

Table 1: Pharmacological Treatment Guidelines for Acute and Delayed Chemotherapy-induced Nausea and Vomiting

Emetic Risk and Timing	High	Anthrocycline + Cyclophosphamide (AC)	Moderate other than AC	Low	Minimal
Acute nausea and vomiting (day one)	5-HT_3 + DEX + NK-1	5-HT_3 + DEX + NK-1	PALO + DEX	DEX or 5-HT_3 or DRA	As needed
Delayed nausea and vomiting (days one to three)	DEX + NK-1	NK-1	DEX	As needed	As needed

5-HT3 = serotonin receptor antagonist; DEX = dexamethosone; DRA = dopamine receptor antagonist; NK-1 = neurokinin-1 receptor antagonist; PALO = palononsetron.

a three-day aprepitant regimen for CINV.[104] The use of aprepitant may also provide an advantage in that patients have to take only one dose of dexamethasone on day one with moderately emetic chemotherapy regimens.[105] Fosaprepitant may offer an option for patients who cannot tolerate oral administration of anti-emetics, particularly during an episode of severe nausea or vomiting.[106]

Guidelines

Clinical practice guidelines for CINV have been developed using evidence-based research by expert panels including the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN), and the Multinational Association of Supportive Care in Cancer (MASCC).[22,107–112] Research shows that adherence to these guidelines can improve complete control of CINV by almost 20 %.[113] Guidelines for anti-emetic usage are based on the potential of experiencing CINV for specific chemotherapy regimens and classify regimens into four categories: highly emetic (>90 %), moderately emetic (both with and without anthracycline and cyclophosphamide [AC]; 30–90 %), low emetic (10–30 %), and minimally emetic (<10 %). The guidelines for anti-emetic use are broken down further into categories based on the patient's expectations (anticipatory), time of onset (acute and delayed), and resistance to anti-emetic treatment (breakthrough and refractory; see *Table 1*). As mentioned previously in this article, anticipatory CINV is an expected or conditioned response that usually occurs just prior to the actual administration of chemotherapy treatment.[12,114,115] Acute CINV usually occurs within the first few hours of chemotherapy administration, peaking between five and six hours and resolving within 24 hours.[116] Delayed CINV occurs more than 24 hours after chemotherapy administration and can last up to seven days. Delayed CINV is common in chemotherapy regimens that involve cisplatin, carboplatin, cyclophosphamide, and/or doxorubicin.[117] Patients receiving multiday chemotherapy regimens are at risk for both acute and delayed CINV depending on the chemotherapeutic agents and the sequence of administration. Breakthrough CINV occurs when prophylactic anti-emetic treatment fails and 'rescue' anti-emetics are required, while refractory CINV occurs when previous anti-emetic regimens have failed in prior chemotherapy treatment cycles. These comprehensive clinical practice guidelines are a valuable tool for oncologists in the prevention and treatment of CINV. A summary of the recommended treatments is provided in *Table 1*.

Summary

Despite advances in pharmaceutical and behavioral therapies and the provision of standard clinical guidelines for effectively managing CINV, patients continue to experience CINV. Although the introduction of 5-HT_3 and NK-1 antagonists has considerably reduced the incidence of CINV, CINV remains a prevalent adverse effect among cancer patients. If oncologists follow the ASCO, NCCN, or MASCC guidelines for the treatment of CINV, research suggests that control of CINV can be improved by approximately 20 %.[113] Evidence also suggests that the addition of integrative therapies including herbal supplements, acupuncture, PMR, guided imagery, hypnosis, and exercise can improve control of anticipatory, acute, and delayed CINV above and beyond what is achieved by the use of pharmaceuticals alone. These integrative behavioral interventions need to be included in standard clinical practice guidelines. CINV as a fearsome adverse effect is more manageable now than in years past with the advent of powerful, long-acting agents. Unfortunately, adequate control of nausea remains a challenge and requires increased research focus. ■

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